REMARKS / ARGUMENTS

In response to the office action of September 11, 2007, Applicant has amended the claims, which when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

Claims 11-22 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cavanak (US 5,639,724) in view of Amselem (US 5,576,016). Cavanak has been cited for teaching pharmaceutical compositions comprising cyclosporine as an active ingredient, a fatty acid triglyceride, a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester and a tenside having an HLB value of at least 10. The examiner notes that the tenside can include polyoxyethylene-sorbitan-fatty acid esters. According to the Examiner, the reference differs from the instant claims insofar as it discloses cyclosporin as the active agent and not a water insoluble drug excluding cyclosporin. Office Action, page 3.

Amselem et al. has been cited for disclosing compositions as carriers for insoluble drugs such as cyclosporine and etopside. The compositions comprise triglycerides, surfactants such as Tween, and phospholipids as well as other components (col. 4, line 23 to col. 9, line 1). It is the position of the Examiner that the reference differs from the instant claims insofar as not disclosing the components in the recited percentages.

Applicant respectfully traverses the rejection for the following reasons. Cavanak teaches use of a glycerol fatty acid partial ester, i.e., a fatty acid **mono**- or **di**-glyceride, or acetylated derivative thereof. *See* Cavanak, column 17, line 42 to column 19, line 33. In contrast, the present claims recite a **poly**glycerol fatty acid ester, not a glycerol fatty acid partial ester or propylene glycol. *See* specification, page 5 to page 6, penultimate paragraph.

Cavanak has also been cited for teaching a sorbitol complete or partial ester. In contrast, the present claims recite a sorbitan fatty acid ester. A sorbitan fatty acid ester is produced by esterification of sorbitol and fatty acid. A sorbitan fatty acid ester has

relatively few free hydroxyl groups while a sorbitol ester has many more hydroxyls and therefore greater stability in water. Thus, Applicant's presently claimed composition with respect to (a) "about 10-50% by weight, based on the carrier composition, of a co-surfactant which is substantially pure or which is in the form of a mixture, having a hydrophilic-lipophilic balance of less than 10 (HLB value according to Griffin), selected from the group consisting of polyglycerol fatty acid esters and sorbitan fatty acid esters" is neither taught nor suggested by Cavanak.

The Examiner has commented that the tenside having an HLB value of at least 10 can include polyoxyethylene-sorbitan-fatty acid esters. Applicants agree that Cavanak teach a polyoxyethylene-sorbitan-fatty acid ester but not as (c) of Cavanak, which requires a sorbitol complete or partial ester, but rather as (e') "a tenside having a hydrophilic-lipophilic balance (HLB) of at least 10." *See* Cavanak, column 13, lines 50-52 and column 14, lines 43-59.

Applicant has also amended claims 11 and 19 to recite the carrier composition "consisting essentially of" (a)–(c) as recited therein. Thus, it is respectfully submitted based on the foregoing remarks that the presently claimed invention is very different from the teaching of Cavanak and respectfully disagree that "the reference differs from the instant claims insofar as it discloses cyclosporin as the active ingredient and not a water insoluble drug excluding cyclosporin" as the Examiner has posited on page 3 of the office action.

Amselem et al. do not cure the deficiency of teachings provided by Cavanak. Amselem et al. teach the use of triglycerides in their "emulsomes". They also teach the use of monoesters, antioxidants, protein components, surface active molecules, phospholipids, etc. Amselem et al. certainly do not teach or suggest Applicant's carrier composition consisting essentially of (a) through (c) as presently claimed.

It is respectfully submitted that even if there was a reason to combine the teachings of Cavanak and Amselem et al. in the manner the Examiner has done, one skilled in the art would still not arrive at Applicant's pharmaceutical composition comprising a solubilized therapeutic agent which is sparingly soluble in water, excluding cyclosporins, and a carrier composition, wherein the carrier composition consists

essentially of a) about 10-50% by weight, based on the carrier composition, of a co-surfactant which is substantially pure or which is in the form of a mixture, having a hydrophilic-lipophilic balance of less than 10 (HLB value according to Griffin), selected from the group consisting of polyglycerol fatty acid esters and sorbitan fatty acid esters; b) about 5-40% by weight, based on the carrier composition, of a pharmaceutically acceptable oil which is substantially pure or which is in the form of a mixture, comprising a triglyceride as essential lipophilic component; and c) about 10-50% by weight, based on the carrier composition, of a nonionic surfactant which is substantially pure or which is in the form of a mixture, having an HLB value of more than 10; and further optional pharmaceutically acceptable excipients. Nor would one skilled in the art have arrived at the specific composition of presently-amended claim 19. Withdrawal of the rejection of claims 11-22 under 35 U.S.C. §103(a) is therefore warranted.

Claims 11-22 have also been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Constantinides (WO 93/02665) in view of Gregory et al. (US 5,262,179). Constantinides has been cited for teaching micro-emulsions comprising a long chain fatty acid triglyceride including neutral oil, low HLB surfactants including long chain fatty acid monoglycerides, high HLB surfactants including polyoxyethylene sorbitan and a *water soluble drug.* The Examiner has asserted on page 4 of the office action that "the reference differs from the instant claims insofar as it does not disclose the drug is water insoluble."

It is respectfully submitted that Constantinides discloses a water-in-oil microemulsion comprising:
(a) a lipophilic phase having a long-chain fatty acid and a low HLB surfactant;
(b) a high HLB surfactant;
(c) an aqueous hydrophilic phase; and
(d) a water-soluble therapeutic agent.

Thus, in the first instance, Constantinides *specifically teaches use of a water-soluble therapeutic agent. See* page 4. In contrast, the presently claimed invention recites a therapeutic agent that is sparingly soluble in water. Moreover, the presently claimed invention does not contain an aqueous hydrophilic phase as does the composition of Constantinides.

Gregory et al. has been cited for teaching the difficulty of delivery ibuprofen, that ibuprofen is water insoluble, often causes gastric irritation when administered in solid or suspended form, especially in doses required to treat rheumatic disease. Gregory et al. has also been cited for disclosing that solutions of water-soluble ibuprofen salts have an unpleasant burning taste and, for that reason, their use generally has been avoided and that many attempts have been made to improve the solubility and taste of ibuprofen especially in free acid form. The Examiner readily admits that the reference does not disclose the surfactant, co-surfactant and oil carrier as recited in the present claims.

Applicant submits that Gregory et al. further teach the surprising finding that inclusion of sodium bicarbonate or potassium bicarbonate in a water-soluble composition containing a water-soluble ibuprofen salt masks the unpleasant taste of ibuprofen in the aqueous solution. *See* Gregory et al. column 2, line 62 to column 3, line 4.

In formulating a rejection under 35 U.S.C.§ 103(a), based upon a combination of prior art elements, it remains necessary to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. *KSR International v. Teleflex, Inc.,* 82 USPQ 2d 1385 (U.S. 2007). It is respectfully submitted that such reasons have not been identified by the Examiner in this case.

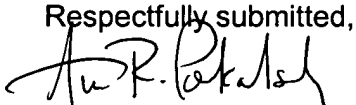
In the first instance, ibuprofen is either insoluble or soluble as a salt. Since Constantinides teaches a microemulsion comprising a water soluble drug, one skilled in the art would not have been motivated to use water-insoluble ibuprofen in the microemulsions of Constantinides. Further, since Gregory et al solves the problem of the unpleasant taste associated with a water-soluble ibuprofen salt, simply by including sodium bicarbonate or potassium bicarbonate, one skilled in the art would not be motivated to look further for ways to improve water-soluble ibuprofen compositions.

Even if there was a reason to combine the two references in the manner the Examiner has done, one skilled in the art would still not arrive at Applicant's invention. There simply is no motivation or suggestion in either of the cited references, taken alone or in combination, for or a pharmaceutical composition comprising a solubilized therapeutic agent which is sparingly soluble in water, excluding cyclosporins, and a

carrier composition, wherein the carrier composition consists essentially of a) about 10-50% by weight, based on the carrier composition, of a co-surfactant which is substantially pure or which is in the form of a mixture, having a hydrophilic-lipophilic balance of less than 10 (HLB value according to Griffin), selected from the group consisting of polyglycerol fatty acid esters and sorbitan fatty acid esters; b) about 5-40% by weight, based on the carrier composition, of a pharmaceutically acceptable oil which is substantially pure or which is in the form of a mixture, comprising a triglyceride as essential lipophilic component; and c) about 10-50% by weight, based on the carrier composition, of a nonionic surfactant which is substantially pure or which is in the form of a mixture, having an HLB value of more than 10; and further optional pharmaceutically acceptable excipients. Nor would one skilled in the art have arrived at the specific composition of presently-amended claim 19. As such, the present invention is not obvious. Withdrawal of the rejection of claims 11-22 under 35 U.S.C. §103(a) is therefore warranted.

In view of the foregoing remarks, it is respectfully submitted that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Ann R. Pokalsky
Reg. No. 34,697
Attorney for Applicants

DILWORTH & BARRESE
333 Earle Ovington Blvd.
Uniondale, NY 11553
(516) 228-8484
ARP/ml